The Approval Process for Clinical Laboratory Devices

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CDRH Mission Statement

….responsible for ensuring that medical devices are safe and effective…..

- Two pronged approach
  - promote public health
  - protect public health

Background

- Federal Food, Drug, and Cosmetic Act of 1938 (The Act)
- Medical Device Amendments of May 28, 1976
- Safe Medical Devices Act of 1990
- FDA Modernization Act (FDAMA) of 1997

Device Classification

Class I

- devices needing the lowest level of regulation
- subject to the general controls
  - requirements sufficient to assure safety and effectiveness for their intended use.

General controls

- registration and listing
- Good Manufacturing Practices (GMPs)
- premarket notification (510(k))
- prohibition of adulterated, misbranded, or banned devices
- record keeping
- reporting of device failures

Device Classification (cont'd)

Class II

- devices subject to special controls in addition to general control requirements.

Special controls

- performance standards
- postmarket surveillance
- patient registries
- guidelines/guidances
- design control
- tracking requirements

Device Classification (cont'd)

Class III

- devices with high risk
- have no established predicates, or
- new device raises new types of questions about safety and effectiveness.

Pathways to Market

- IVD may be exempt
- Premarket notification - 510(k)
- Premarket approval - PMA
  - "significant risk" devices require an Investigational Device Exemption - IDE
- Product development protocol - PDP
- Humanitarian device exemption - HDE
- Analyte specific reagent - ASR

510(k) Process

- Section 510(k) of the FD&C Act
- Demonstrates "substantially equivalent"
  - same intended use
  - similar technological characteristics
  - does not raise new issues of safety and effectiveness
- 90-day review clock

PMA Process

- Class III devices are subject to premarket approval requirements
- Reasonable assurance of safety and effectiveness
- 180 day review timeframe

PMA Process (cont'd)

The review of a PMA is a 4-step process consisting of:

- Filing review
- In-depth review
- Panel review (if necessary)
- Final Decision

Limitations in Review

- Paper review
- Lack of performance standards
- Lack of “gold standards”
- Bias

Major Elements of a Submission

- Intended use/indications for use
- Performance characteristics
- Labeling (package insert)

Performance Characteristics Non-clinical Studies

Characterization of components

- Antigens/antibodies
- Controls/calibrators
- Cut-off determination
- Equivocal zone

Performance Characteristics Non-clinical Studies (cont'd)

- Accuracy
  - performance of test vs. analytical standard (bias)
- Analytical sensitivity
  - lowest detectable level of analyte
- Analytical specificity
  - interference, cross-reactivity

Performance Characteristics Non-clinical Studies (cont'd)

- Specimen handling
  - fresh, frozen, centrifugation, etc
- Linearity
  - range where there's direct relationship between analyte and target
  - reportable range

Performance Characteristics Non-clinical Studies (cont'd)

Precision-reproducibility of a test when it is run several times (CV)

- Intra-assay
- Inter-assay
- Inter-laboratory
- Lot-to-lot
- Inter-technician (POC)

Clinical Protocol

- Objectives
- Developed in advance
- Patient recruitment procedures
- Patient / specimen inclusion / exclusion criteria
- Sample size
- End points
- Gold standard

Performance Characteristics Clinical Studies

- Clinical sensitivity--the ability of the test to correctly identify the presence of disease.

- Clinical specificity--the ability of the test to correctly identify the absence of disease.

Simple Model

Clinical Truth

2 outcomes

"**Diseased**"		"**Non-Diseased**"
Condition/Analyte Present	**OR**	Condition/Analyte Absent
Case +		Case –

Clinical "Truth"

- "gold standard" or 100% accurate method
- clearly defined clinical criteria, signs & symptoms
- some combination

Example

		TRUTH	
		Diseased +	Non-diseased –
New	+	44	1
Test	–	7	168
total		51	169

estimated sensitivity = 44/51 or 86.3%

estimated specificity = 168/169 or 99.4%

Same Example

		Imperfect Standard +	Imperfect Standard –
New	+	40	5
Test	–	4	171
total		44	176

Can't get sensitivity and specificity (no truth)

overall agreement = (40+171)/220 = 211/220 or 95.9%

Problem with Agreement

AGREEMENT ≠ CORRECT

Concrete Example

- Cystatin C
  - compared to creatinine as a predicate for "substantial equivalence"
    - BUT
  - had to compare to iothalamate clearance /GFR (clinical truth) to compute sensitivity and specificity

Statistical Comparison of Cystatin C and Creatinine

	Cystatin C (95% CI)	Creatinine (95% CI)
Sensitivity (%)	94 (91,96)	81 (77,85)
Specificity (%)	82 (76,89)	88 (83,94)
PPV (%)	93 (91,96)	95 (92,97)
NPV (%)	83 (77, 89)	64 (57,71)

Another Example

- Agreement of PSA results at a cutoff of 4 ng/ml

	New PSA test			
Established PSA test	≥ 4	<4	Total	
≥ 4	349	22	371	70.4% ± 1.99%
<4	8	148	156	
Total	357	170	527	

67.7% ± 2.0%

Observed Agreement	94.3%	Chance agreement	57.2%
Difference in test positivity		-2.7%	± 1.0%

Statistical Comparison of a New and Established PSA test

Agreement when clinical status is known: Cancer Subjects

	New PSA test			
Established PSA test	≥ 4	<4	Total	
≥ 4	208	11	219	94.8% ± 1.46%
<4	2	10	12	
Total	210	21	231	
	90.9% ± 1.9%			

Observed Agreement 94.4% Chance agreement 86.7%

Difference in Sensitivity -3.9% ± 1.5% p = 0.011 of Equal Se

Difference in Specificity -3.5% ± 2.3% p > 0.05 of Equal Sp

Another Example

- Cyclosporine Assays
  - due to variability of immunoassays, discourage comparison to each other
  - encourage comparison to HPLC or tandem mass spectroscopy
    i.e., clinical truth is parent compound

Another Example

- Monitoring overall immune status
  - currently no single test for adequate comparison, therefore:
    - need to compare to patients clinical state: rejecting (undersuppressed), infected (overly suppressed), good allograft function
    - would values change quickly enough to be useful for clinical monitoring

Some Key Statistical Points

- You can compute estimated sensitivity and specificity of the new test only if you know truth and the new test results for all patients.

- Don't use the terms sensitivity and specificity to describe the comparison of a new test to an imperfect standard. Instead, report the agreement between the two methods.

Key Statistical Points (cont'd)

- Don't revise results based on discrepant resolution alone - misleading and biased
- There are valid statistical alternatives to discrepant resolution for estimating sensitivity and specificity when a perfect standard exists (FDA guidance document pending).
- There are no simple statistical solutions for obtaining unbiased sensitivity and specificity estimates when no perfect standard exists - more research is needed.

Safety & Efficacy

- Risk : Benefit
  - impact of an erroneous result?
    - false positive
    - false negative
    - screening vs. diagnosis
    - stand alone vs. adjunct

Labeling of IVDs (21 CFR 809.10(b))

- Proprietary and established names
- Intended Use(s)
- Summary and explanation of test
- Principle of procedures
- Information on reagents
- Information on instruments
- Specimen collection and preparation
- Warnings and limitations

Partnerships

- Encourage partnerships with CDC, NIH, WHO etc. and sponsors
- Need for a panel of well-characterized specimens
- Encourage early collaboration
- Evaluate protocols
- Develop guidance and standards documents

Impact on Patient Care

- Ensure device performance meets a minimum threshold
- ensure truth in labeling
- ensure accountability for consistent manufacturing in conformance with labeling claims
- ensure adverse events are reported, tracked and corrective action taken

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